UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/622,284	08/15/2000	Takumi Sasaki	20-4736P	9843

2292 7590 10/06/2003

BIRCH STEWART KOLASCH & BIRCH
PO BOX 747
FALLS CHURCH, VA 22040-0747

EXAMINER	
DEVI, SARVAMANGALA J N	

ART UNIT	PAPER NUMBER
1645	

DATE MAILED: 10/06/2003

12

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/622,284	Applicant(s) Sasaki et al.
	Examiner S. Devi, Ph.D.	Art Unit 1645

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Jul 24, 2003*.

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-13* is/are pending in the application.

4a) Of the above, claim(s) *6 and 7* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-5 and 8-13* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☒ The specification is objected to by the Examiner.

10) ☒ The drawing(s) filed on *Aug 15, 2000* is/are a) ☒ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☒ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). *3 and 4*.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Preliminary Amendments

1) Acknowledgment is made of Applicants' preliminary amendments filed 07/19/02 (paper no. 6) and 10/21/02 (paper no. 8).

Election

2) Acknowledgment is made of Applicants' election filed 07/24/03 (paper no. 10) in response to the written lack of unity mailed 06/24/03 (paper no. 9). Applicants have elected invention I, claims 2-5 and 8-13. Because Applicants did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (M.P.E.P § 818.03(a)).

Status of Claims

3) Claims 1-13 are pending.

Claims 6 and 7 have been withdrawn from consideration as being directed to a non-elected invention. See 37 C.F.R 1.142(b) and M.P.E.P § 821.03.

Elected claims 2-5 and 8-13 and the linking claim 1 are under examination. A First Action on the Merits is issued on these claims.

Information Disclosure Statements

4) Acknowledgment is made Applicants' Information Disclosure Statements filed 08/15/00 and 11/14/00 (paper no. 3 and 4). The information referred to therein has been considered and a signed copy is attached to this Office Action (paper no. 12).

Sequence Listing

5) Acknowledgment is made of Applicants' submission of CRF and the raw Sequence Listing which have been entered 07/30/02.

Drawings

6) The drawings submitted in the instant application is not objected to by the Draftsperson under 37 C.F.R 1.84 or 1.152 and as such, the drawings have been approved as formal drawings.

Priority

7) The instant application is a national stage 371 application of PCT/JP99/00638, filed 02/15/1999 and *claims priority to the foreign application, 0501371998, filed 02/15/1998 in*

Japan.

It is noted that a copy of the non-translated priority document has been submitted to the Office.

Abstract

8) The abstract of the disclosure is objected to because the recitation "said" is legal phraseology and should be avoided. Correction is required. See M.P.E.P 608.01(b).

Specification - Informalities

9) The instant specification is objected to because:

(a) The first paragraph of the specification does not accurately reflect the status of the prior application, as indicated above in italicized letters under 'Priority'.

(b) The use of the trademarks in the instant specification has been noted in this application. For example, see line 2 on page 26: "Sepharose"; and page 21, line 14: "Invitrogen". Although the use of trademarks is permissible in patent applications, the propriety nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks. It is suggested that Applicants examine the whole specification and make necessary changes wherever trademark recitations appear.

Rejection(s) under 35 U.S.C. § 112, First Paragraph

10) Claims 1-5 and 8-13 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

The recitation 'derivatives thereof' in the instant claims is interpreted as encompassing derivatives of SEB or derivatives of modified SEB. It is noted that the 'derivatives' recited in the instant claims do not exist independent of their function(s), i.e., inhibitory activity on T cell activation, interaction with specific Vβ component of T cell receptor (TCR), reduced immunological responsiveness, and prophylactic activity against immunopathy, including rheumatoid arthritis. The specification discloses prophylactic or therapeutic applications or intentions for the claimed 'derivatives'. However, the instant specification fails to teach a single derivative of SEB or derivative of modified SEB having the above-cited functional activities.

Prophylactic or therapeutic applications minimally require a specific inhibitory action of derivatives on T cell activation and reduced immunological responsiveness. The precise structure or relevant identifying characteristics of each 'derivative' of SEB or modified SEB having the above-cited functional activities can only be determined empirically by actually making every DNA molecule that encodes the 'derivative', and testing each DNA molecule to determine whether it encodes the 'derivative' having the particularly disclosed biological activities. The *Written Description Guidelines* state:

> There is an inverse correlation between the level of predictability in the art and the amount of disclosure necessary to satisfy the written description requirement. For example, if there is a well-established correlation between the structure and function in the art, one skilled in the art will be able to reasonably predict the complete structure of the claimed invention from its function.

A mere statement in the specification that the invention includes the use of such a 'derivative' as a prophylactic or remedy for immunopathy is insufficient to meet the adequate written description requirement of the claimed invention. The SEB molecule has specific functional or biologic properties dictated by the structure of the toxin and the corresponding structure of the gene sequence which encodes it. A convincing structure-function relationship has to exist between the structure of the gene sequence, the structure of the toxin derivative encoded, and the function of the encoded toxin derivative. The function cannot be predicted from the modification of the structure of the gene and in the instant case, the DNA encoding the 'derivative' of SEB or 'derivative' of modified SEB. Applicants have not shown that derivatization of a reference gene sequence encoding a reference SEB as claimed would automatically predict the production of a SEB 'derivative' having the recited functional activities. The specification fails to teach the structure or relevant identifying characteristics of a representative number of species of DNA molecules encoding a representative number of species of 'derivatives' of SEB or 'derivatives' of modified SEB as recited, sufficient to allow one skilled in the art to determine that the inventors had possession of the invention as claimed. With the exception of a modified SEB having specific amino acid substitutions, for example, at position 9, 23 or 44 of a native staphylococcal SEB, a skilled artisan cannot envision the detailed chemical structure of all the 'derivative' species encompassed by the recited molecule. Regardless of the complexity or simplicity of the method of isolation, conception cannot be achieved until reduction to practice has occurred. Adequate

written description requires more than a mere statement that its is a part of the invention and a reference to a potential method of isolating it. The 'derivatives' of SEB or 'derivatives' of modified SEB, or the DNAs encoding the 'derivatives' themselves are required. See *Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993)* and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016.*

Rejection(s) under 35 U.S.C. § 112, Second Paragraph

11) The following is a quotation of the second paragraph of 35 U.S.C. § 112:

> The specification shall conclude one or more claims particularly pointing out and distinctly claiming the subject matter which the Applicant regards as his/her invention.

12) The claims of the instant application are very poorly written. With the unclear claim language used currently, it is hard to understand the scope of the claims. Applicants are asked to pay close attention to the following comments and/or suggestions while amending the claims.

13) Claims 1-5 and 8-13 are rejected under 35 U.S.C § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

(a) Claim 1 is vague and indefinite in the recitation: 'comprising, as an active ingredient, modifications of ..... SEB ...'. An ingredient can be a modified product. An ingredient cannot be referred to as 'modifications', since a 'modification' represents a process, not a product.

(b) Claim 1 is vague and indefinite because, the claimed remedy is recited as : 'comprising, as an active ingredient, modifications of ..... SEB ...' [Emphasis added]. Does it mean that the claimed product is a mixture of multiple molecules of modified SEBs, or one molecule of SEB with multiple modifications within the molecule?

(c) Claims 2 and 3 are vague and indefinite in the recitation: 'said SEB modifications or derivatives thereof are SEB having amino acid substitution at the 9-position' [Emphasis added]. It is unclear how substitution at one position can be called 'modifications' as opposed to a modification.

(d) Claims 4 and 5 are vague and indefinite in the recitation: 'said SEB modifications or derivatives thereof are SEB having amino acid substitution at the 23-position' [Emphasis

added]. It is unclear how substitution at one position can be called 'modifications' as opposed to a modification.

(e) Claims 8 and 9 are vague and indefinite in the recitation: 'said SEB modifications or derivatives thereof are SEB having amino acid substitution at the 44-position' [Emphasis added]. It is unclear how substitution at one position can be called 'modifications' as opposed to a modification.

(f) Claims 1-5, 8 and 9 are vague and indefinite in the recitation "derivatives", because it is unclear what is encompassed in this recitation. What constitutes a derivative, and how much of the SEB's or modified SEB's original structure has to be retained such that the resulting product can be considered as a 'derivative', is not clear. The metes and bounds of the structure encompassed in the limitation 'derivative' is indeterminate.

(g) Claim 1 is vague and indefinite in the recitations: 'natural type SEB' and 'wild-type SEB'. It is unclear how the two SEBs differ from one another structurally or functionally.

(h) Claim 1 is vague in the use of the non-legal language: 'they' (see line 7).

(i) Claims 2-5, 8 and 9 are vague and confusing in the recitation: 'substitution ..... on the basis of natural type SEB', because it is unclear what is meant by 'substitution on the basis of natural type SEB'. Does it mean that the recited substitution is in the natural type SEB?

(j) Claim 13 is indefinite in that it includes non-elected subject matter.

(k) Claims 2-5 and 8-13, which depend directly or indirectly from claim 1, also stand rejected under 35 U.S.C § 112, second paragraph, because of the vagueness or indefiniteness identified above in the base claim.

Rejection(s) under 35 U.S.C. § 102

14) The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> **(b)** the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

15) Claims 1 and 13 are rejected under 35 U.S.C. § 102(b) as being anticipated by the Canadian patent 2,084,120A1 (31 May 1994) or Bill Jerome *et al.* (WO 96/40235).

The Canadian patent 2,084,120A1 disclosed a remedy for autoimmune diseases, such as, rheumatoid arthritis, multiple sclerosis, systemic lupus erythematosus, type I diabetes etc., comprising a derivative, analogue or a fragment of staphylococcal enterotoxin B or SEB, which is effective in inactivating and/or reducing the number of T cells that express Vβ T cell receptor and decrease the disease activity (see claims). The SEB derivatives or analogues are SEB molecules having additions, deletions or replacements of amino acids (see pages 6 and 7).

Bill Jerome *et al.* disclosed a remedy for T cell-mediated diseases, such as, rheumatoid arthritis, comprising the modified or mutated staphylococcal superantigen enterotoxin B (SEB) which specifically targets the pathogenic Vβ expressing T cells for subsequent inactivation or deletion. The SEB derivatives are substantially identical to the amino acid sequence of an SEB, but altered relative to the native SEB with one or more modifications or mutations (see claims; and pages 15-17).

Claims 1 and 13 are anticipated by the Canadian patent 2,084,120A1 or Bill Jerome *et al.*

16) Claims 1-5 and 8-13 are rejected under 35 U.S.C. § 102(b) as being anticipated by Kappler *et al.* (WO 93/14634 - Applicants' IDS).

Because of the poor claim language used, the scope of the claims is not clearly understood. Claims 2 and 3 are interpreted in this rejection as being directed to a modified or mutant staphylococcal enterotoxin B (SEB) having a mutation at position 9 of the SEB wherein any amino acid other than aspartic acid is substituted. Claims 4 and 5 are interpreted for the purpose of this rejection as being directed to a modified or mutant SEB having a mutation at position 23 of the SEB wherein any amino acid other than asparagine is substituted. Similarly, claims 8 and 9 are interpreted in this rejection as being directed to a modified or mutant SEB having a mutation at position 44 of the SEB wherein any amino acid other than phenylalanine is substituted.

Kappler *et al.* disclosed purified modified superantigens, i.e., staphylococcal enterotoxin B (SEB) mutants, for prevention or treatment of toxic effects of superantigen, and vaccines comprising the same, wherein the mutant superantigens interact with specific Vβ elements of T cell receptors (TCR) and elicit immune response without inducing T cell proliferation. See abstract; claims; and page 16, lines 25-29. Kappler's SEB mutants, BC-6, BC-66 and BC-88,

carried isoleucine, tyrosine and lysine residues respectively at position 23 of SEB, whereas the mutant BR-291 carried serine at position 23 of SEB (see Tables II and III; and page 27). While Kappler's SEB mutants, BR-267 and BA-50, carried serine at position 44 of SEB, the mutant BA-53 carried leucine at position 43 of SEB (see Tables II and III). Kappler *et al.* also disclosed a SEB mutant, BR-257, which carried asparagine in place of aspartic acid at position 9 of SEB (see Figure 3 and last paragraph on page 27). Kappler's SEB mutants were protective when administered to monkeys and mice. The SEB mutants were ineffective or less effective in inducing an emetic response in monkeys compared to wild-type SEB (see pages 35 and 38; and Example 8). Mice and primates receiving the SEB mutant, BR-257, were fully protected from the toxic effects of SEB (see page 21). Kappler *et al.* taught of the causation of autoimmune diseases, such as, rheumatoid arthritis by natural superantigens and amelioration of such diseases in patients by partial elimination or inhibition of T cells bearing Vβ components (see paragraph bridging pages 6 and 7 as well as pages 7 and 8; first full paragraph on page 7; and second full paragraph on page 10). Kappler *et al.* taught that the amino acid residue 23N is an important amino acid for Vβ interaction and that 44F is important in binding of the SEB to class II MHC (see page 32, lines 25 and 26; page 31, lines 28, 29, 32 and 33; page 30, first paragraph; and page 20, last paragraph). The prior art vaccine formulation meant for active immunological prophylaxis and administration may contain adjuvants, carriers, or other materials (see page 16, lines 25-29; and last two paragraphs on page 18). The mode of administration may include all of the standard methods of administering therapeutic agents to a subject (see first paragraph on page 19) and therefore includes oral administration. That the prior art SEB mutants were administered *in vivo* to mice and monkeys (see page 21) indicates that the mutants were contained in a solution of physiologically acceptable tonicity. The purified mutant SEB was contained in saline, balanced salt solution, or glycine (i.e., amino acid)-HCl solution neutralized with sodium carbonate (see pages 27 and 34; and Example 7).

Claims 1-5 and 8-13 are anticipated by Kappler *et al.*

Remarks

17) Claims 1-5 and 8-13 stand rejected.

18) Papers related to this application may be submitted to Group 1600, AU 1645 by facsimile

transmission. Papers should be transmitted via the PTO Fax Center located in Crystal Mall 1. The transmission of such papers by facsimile must conform with the notice published in the Official Gazette, 1096 OG 30, November 15, 1989. The CM1 facsimile center's telephone number is (703) 308-4242, which is able to receive transmissions 24 hours a day and 7 days a week. The RightFax number for submission of before-final amendments is (703) 872-9306. The RightFax number for submission of after-final amendments is (703) 872-9307.

19) Any inquiry concerning this communication or earlier communications from the Examiner should be directed to S. Devi, Ph.D., whose telephone number is (703) 308-9347. The Examiner can normally be reached on Monday to Friday from 7.45 a.m. to 4.15 p.m. except one day each bi-week, which would be disclosed on the Examiner's voice mail system. A message may be left on the Examiner's voice mail system.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Lynette Smith, can be reached on (703) 308-3909.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

October, 2003

S. DEVI, PH.D.
PRIMARY EXAMINER